claims 21-23, 33, 42 and 45 can be found, inter alia, in the specification at paragraphs [0058] and [0059]. Support for new claims 25 and 47 can be found, inter alia, in Figures 8-15 of the specification and original claim 6. Support for new claims 18-20, 24, 26-30, 34, 39, 42-46 and 48-53, inter alia, can be found in originally filed claims 3-11. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and request that they be withdrawn. Applicants respectfully request that the application be deemed sufficient for allowance.

Rejections under 35 U.S.C. § 112, first paragraph, written description

The Examiner has rejected claims 1-11 under 35 U.S.C. § 112, first paragraph, for allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." Paper No. 10, page 2. According to the Examiner, "the specification does not disclose any of the claimed variants or modifications, nor does it provide any teachings as to how the structures of these sequences relate to their function." Paper No. 10, page 2. The Examiner also alleges that the specification "does not describe the complete structure of a representative number of species of the claimed genuses." Paper No. 10, page 2. Applicants respectfully disagree and traverse the rejection as it may apply to the present claims.

The test for the written description requirement is whether one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention in the

specification as filed. *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02.

Applicants point out that the Federal Circuit stated in *Univ. of Calif. v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), that:

> A description of a genus of cDNAs may be achieved by means of a recitation of [1] a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or [2] of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. . . . We will not speculate in what other ways a broad genus of genetic material may be properly described, . . .

Univ. of Calif., 43 U.S.P.Q.2d at 1406. Thus, the Federal Circuit has stated that the written description requirement for a claim directed to a genus of cDNAs may be satisfied by providing the sequences of a representative number of cDNAs which fall within the scope of the genus or by providing a recitation of structural features which are common to a substantial portion of the members of the genus. *See Univ. of Calif.*, 43 U.S.P.Q.2d at 1406. Thus, in order to fall within the scope of the genus, the DNA sequence must have specific functional or structural characteristics.

New claims 12-53 are directed to methods of producing recombinant heterologous proteins such as tPA, K2S, or functional variants or derivatives thereof. Applicants assert that a number of species which fall within the scope of the genus are described in the captioned application as discussed below.

Contrary to the Examiner's position, the specification discloses functional variants or derivatives of heterogous proteins. For example, domains or subunits or variants of tPA are disclosed. These domains of tPA include: the finger domain, the growth factor domain,

the Kringle 1 domain, the Kringle 2 domain, the protease domain, and the Kringle 2 plus serine protease (K2S) domain. *See* Specification, page 14, paragraphs [0058] and [0059].

The specification also discloses variants of K2S. These variants of K2S include: 1) amino acids 174-527 (SEQ ID NO:10); 2) amino acids 197-527 (SEQ ID NO:11); 3) amino acids 193-527 specifically modified to include the amino acid sequence SEGN at the N-terminus (SEQ ID NO:12); 3) amino acids 193-527 specifically modified to change the Cys at position 261 to a Ser (SEQ ID NO:13); 4) amino acids 191-527 specifically modified to change the Cys at position 261 to a Ser (SEQ ID NO:13); 5) amino acids 220-527 (SEQ ID NO:16); and 6) amino acids 260-527 (SEQ ID NO:17). *See* Specification, paragraphs [0021]-[0029] and Figures 8-15.

Figures 8-15 denote the predicted secondary structures of these variants and indicate that the variants share common structural characteristics. For example, the variant of K2S represented in Figure 11, shares common structural characteristics with the corresponding wild-type K2S structure shown in Figure 9. The modification shown in Figure 11, which changes the Cys at position 261 to a Ser within amino acids 193-527 (SEQ ID NO:13), does not alter the structure of the K2S domain in comparison to the wild-type K2S structure shown in Figure 9. Similarly, the variants of K2S shown in Figures 8, 10, and 12-15 also form similar secondary structures to each other and to the wild-type K2S structure shown in Figure 9. *See* Specification, Figures 8-15. Thus, these variants share common structural characteristics.

Applicants assert that the written description requirement is satisfied. The application discloses a representative number of species of heterologous protein which fall within the scope of the genus. Applicants have also shown that variants of the heterologous protein

K2S share common structural characteristics. Thus, Applicants have conveyed with reasonable clarity to those skilled in the art that they were in possession of the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112 be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph, enablement

The Examiner has rejected claim 8 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement as containing subject matter, "which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Paper No. 10, page 3. Specifically, the Examiner claims that "[i]n order to sufficiently enable the claimed phagemid, Applicant must make a biological deposit." Paper No. 10, page 4. Applicants respectfully request that this rejection be withdrawn based on the remarks below.

Applicants have cancelled claim 8 and added new claims 27 and 50 which recite the pComb3HSS phagemid. According to the requirements for the deposit of biological material, the biological material need not be deposited, inter alia, if it can be made or isolated without undue experimentation. 37 C.F.R. § 1.802(b) (2003).

Based on the description of pComb3HSS in the specification and based on guidance in the art, Applicants argue that the claims are sufficiently enabled, and that a vector comprising pComb3HSS can be made without undue experimentation. The pComb3HSS phagemid was provided to the inventors of the present application by Dr. Carlos F. Barbas, Scripps Institute, USA. *See* Specification, paragraph [0065]. The inventors of the current

application utilized this vector to construct pComb3H-K2S. The pComb3H-K2S construct is a vector comprising pComb3HSS in that it is simply the pComb3HSS phagemid with the K2S sequence inserted into it. *See* Specification, paragraph [0065]. If one were to delete the K2S sequence from the pComb3H-K2S construct, the result would be the pComb3HSS phagemid. The deletion of the K2S insert can be easily performed by digestion with a restriction endonuclease using standard molecular biology cloning techniques.

The specification also discloses a map of a vector comprising pComb3HSS with K2S inserted into it. *See* Specification, Figure 4. This map provides the locations of key elements of pComb3HSS such as the lac operon, the ribosomal binding site, the gpIII gene, and the ampicillin resistance gene. The regions which these elements span are indicated by the numbering of the nucleotide sequences within the vector. *See* Specification, Figure 4. Thus, the specification provides disclosure sufficient for claims 27 and 50 to be enabled.

In addition, one skilled in the art could use disclosure in the specification coupled with disclosure in the art to make a vector comprising the pComb3HSS phagemid without undue experimentation. The vector comprising pComb3HSS can be made by modification of the pComb3 vector. The pComb3 vector is disclosed and described in "Assembly of combinatorial antibody libraries on phage surfaces: The gene III site, " Barbas, *et al.*, *Proc. Natl. Acad. Sci. USA 88*: 7978-7982 (1991) (cited as Document AT1 in the IDS filed August 20, 2002). The construction of pComb3 is described in detail in the "Materials and Methods" section. Barbas at 7978. This section indicates how the vector was cloned and what sources were used to obtain fragments which were ligated together to generate pComb3, the backbone utilized to construct the phagemid of the claimed invention.

Finally, elements of the pComb3HSS phagemid are well known in the art. The sequences of these elements are readily available or can be made by one skilled in the art. One skilled in the art would know how to manipulate these elements using standard DNA techniques, together with the publicly available pComb3 vector backbone, to construct a vector comprising pComb3HSS.

Thus, based on the disclosure in the specification and in the art, one of skill in the art could make and use a vector comprising the pComb3HSS phagemid without undue experimentation. The disclosure provides a map diagramming the elements of pComb3HSS. Additionally, the elements of pComb3HSS were available in the art. One of skill in the art, using the information described above and standard cloning techniques in molecular biology, could readily make and use the recited vector comprising the pComb3HSS phagemid. Accordingly, Applicants assert that the claimed invention is sufficiently enabled and respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1 and 3 under 35 U.S.C. § 102(b) as allegedly being anticipated by Sivaprasadarao *et al.* (*Biochemical Journal 296*: 209-215 (1993)). Paper No. 10, page 4. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). MPEP § 2131.

Applicants assert that the present claims are not anticipated by Sivaprasadarao *et al.* Sivaprasadarao *et al.* disclose expression of the OmpA-retinol-binding (RBP) fusion protein.

Applicants have cancelled claims 1 and 3 and added new claims 12-53. New claims 12-30 are generally directed to a method for the production of a recombinant heterologous fusion protein comprising a heterologous protein, the OmpA signal peptide, *and* additionally comprising either the signal peptide sequence SEGN or SEGNSD. The rejection under 35 U.S.C. § 102(b) has thus been rendered moot. Sivaprasadarao *et al.* do not disclose a fusion protein which comprises the peptides SEGN or SEGNSD. Thus, new claims 12-30 are not anticipated by Sivaprasadarao *et al.*

New claims 31-53 are generally directed to a method for the production of a recombinant fusion protein comprising tissue plasminogen activator and the OmpA signal peptide. Sivaprasadarao *et al.* disclose expression of a fusion protein comprising retinol-binding protein and the OmpA signal peptide, but not a fusion protein comprising tissue plasminogen activator and the OmpA signal peptide. Because Sivaprasadarao *et al.* does not disclose every element of claims 31-53, these claims are not anticipated by Sivaprasadarao *et al.* Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1 and 2 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sivaprasadarao *et al.* in view of Accession No. E02814. Paper No. 10, page 5. In order to establish a *prima facie* case of obviousness, the references, when combined, must teach or suggest all the claim limitations. MPEP § 2143. Based on the arguments above, Applicants assert that the pending claims are not rendered obvious in view of the above-listed references.

New claims 12-30 are generally directed to a method for the production of a recombinant heterologous fusion protein comprising a heterologous protein, the OmpA signal peptide, *and* additionally comprising either the signal peptide sequence SEGN or SEGNSD. Sivaprasadarao *et al.* do not teach the use of a fusion protein comprising either the signal peptide sequence SEGN or SEGNSD. The reference listed as Accession No. E02814, disclosing the DNA sequence coding for the signal peptide OmpA, does not rescue this deficiency. Thus Sivaprasadarao *et al.* in view of Accession No. E02814 do not render claims 12-30 obvious as they do not teach or suggest all of the limitations of the claims.

New claims 31-53 are directed to a method for the production of a recombinant fusion protein comprising tissue plasminogen activator and the OmpA signal peptide. Sivaprasadarao *et al.* disclose expression of a fusion protein comprising retinol-binding protein and the OmpA signal peptide, but not a fusion protein comprising tissue plasminogen activator and the OmpA signal peptide. Accession No. E02814 does not rescue this deficiency as it merely teaches the sequence of the OmpA signal peptide.

As stated in the specification the present invention offers the advantage that an OmpA-tissue plasminogen activator fusion protein would be secreted as an active protein extracellularly; such a method was previously unknown in the art. *See* Specification, paragraphs [0008]-[0009] and [0037]. Sivaprasadarao *et al.* only discuss the secretion of an OmpA-RBP fusion protein into the periplasmic space of a prokaryotic cell, and do not teach secretion of an active protein extracellularly. Thus, Sivaprasadarao *et al.* would not have rendered the claimed invention obvious. Accession No. E02814 does not rescue this deficiency as it merely teaches the sequence of the OmpA signal peptide.

Based on the remarks above, Sivaprasadarao *et al.* in view of Accession No. E02814 do not render claims 12-53 obvious as they do not teach or suggest all of the limitations of the claims. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Conclusion

Prompt and favorable consideration of this Amendment is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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